



## **Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV.**

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# Progressive Multifocal Leukoencephalopathy/JC Virus Infection

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## Epidemiology

Progressive multifocal leukoencephalopathy (PML) is an opportunistic infection of the central nervous system (CNS), caused by the polyoma virus JC virus (JCV) and characterized by focal demyelination.<sup>1,2</sup> The virus has worldwide distribution, with a seroprevalence of 39% to 69% among adults.<sup>3-6</sup> Primary JCV infection usually occurs asymptotically in childhood resulting in a chronic asymptomatic carrier state in most individuals. Viral DNA is detected in 20% to 30% of immunologically normal adults' urine.<sup>4,7-11</sup>

Outside the context of HIV infection, PML is rare and characteristically manifests as a complication of other immunocompromising diseases or therapies.<sup>12-14</sup> In recent years, PML has been reported in patients treated with immunomodulatory humanized antibodies, including natalizumab,<sup>15</sup> efalizumab,<sup>16,17</sup> and rituximab.<sup>18</sup> Concern has been raised about a possible increased risk of PML in HIV-infected patients treated with rituximab for non-Hodgkin lymphoma,<sup>19,20</sup> but no reports have yet documented PML in that setting. Chronic immunosuppression after organ transplantation is occasionally complicated by PML with a very guarded prognosis.<sup>21</sup>

Before the advent of combination antiretroviral therapy (ART), PML developed in 3% to 7% of patients with AIDS<sup>22-24</sup> and was almost invariably fatal; spontaneous remissions were rare.<sup>25</sup> With the widespread use of ART in the developed world, incidence of PML has decreased substantially,<sup>26,27</sup> and mortality in HIV-infected persons who develop the disease has declined.<sup>28-30</sup> Although most CNS opportunistic infections are almost wholly prevented when CD4 T-lymphocyte (CD4 cell) counts are maintained above 100 to 200 cells/mm<sup>3</sup> PML can still sometimes occur in patients treated effectively with ART.<sup>2,31,32</sup> PML can also develop in the setting of initiating ART and immune reconstitution, discussed below.<sup>2,30,33</sup>

## Clinical Manifestations

PML manifests as focal neurological deficits, usually with insidious onset and steady progression. Because the demyelinating lesions can involve different brain regions, specific deficits vary from patient to patient. Any region of the CNS can be involved, although some areas seem to be more favored, including the occipital lobes (with hemianopsia), frontal and parietal lobes (aphasia, hemiparesis, and hemisensory deficits), and cerebellar peduncles and deep white matter (dysmetria and ataxia).<sup>12</sup> Spinal cord involvement is rare and the optic nerves are not involved.<sup>34</sup> Although lesions can be multiple, one is often clinically predominant. Initial symptoms and signs usually begin as partial deficits (e.g., weakness in one leg) that worsen over time and involve a larger territory (e.g., evolution to hemiparesis) as individual lesions expand concentrically or along white matter tracts. The focal or multifocal nature of the pathology is responsible for the consistency of clinical presentations with distinct focal symptoms and signs, rather than as a more diffuse encephalopathy, or isolated dementia or behavioral syndrome, all of which are uncommon without concomitant focal findings.<sup>35</sup>

The time course of this evolving demyelination, with clinical progression over several weeks, often provides a clue to diagnosis because the other major opportunistic focal brain disorders (cerebral toxoplasmosis and primary CNS lymphoma) characteristically progress in hours to days and cerebral infarcts begin even more abruptly. Nonetheless, PML is sometimes mistaken for an evolving stroke, which like PML is bright on diffusion weighted MRI. While rather sudden onset of a focal brain lesion can mimic strokes, the gradually progressive course should rapidly make this diagnosis unlikely with subsequent diagnostic evaluations undertaken to identify PML. Headache and fever are not characteristic of the disease, and when present may indicate presence of another opportunistic infection. Seizures develop in nearly 20% of PML patients and are associated with lesions immediately adjacent to the cortex.<sup>36,37</sup>

## Diagnosis

Initial recognition of PML relies on a combination of clinical and neuroimaging findings: steady progression of focal neurological deficits with magnetic resonance imaging (MRI) almost always demonstrating distinct white matter lesions in areas of the brain corresponding to the clinical deficits. The lesions are hyperintense (white) on T2-weighted and fluid attenuated inversion recovery sequences and hypointense (dark) on T1-weighted sequences.<sup>2</sup> The T1 findings can be subtle and help distinguish lesions due to PML from other pathologies, including the white matter lesions of HIV encephalitis. In contrast to cerebral toxoplasmosis and primary CNS lymphoma, no mass effect or displacement of normal structures is usually evident. Although contrast enhancement is present in 10% to 15% of cases, it is usually sparse with a thin or reticulated appearance adjacent to the edge of the lesions. Exceptions to these characteristic imaging findings can occur when the inflammatory form of PML develops in the setting of immune reconstitution after initiation of ART (see below). Advanced neuroimaging techniques, such as diffusion-weighted imaging and magnetic resonance (MR) spectroscopy, may provide additional diagnostic information.<sup>38-40</sup> New PML lesions and the advancing edge of large lesions have high signal on diffusion-weighted imaging and normal-to-low apparent diffusion coefficient signifying restricted diffusion. These changes relate to regions of active infection and oligodendrocyte swelling. MR spectroscopy can show areas of decreased N-acetylaspartate and increased choline related to axonal loss and cell membrane and myelin breakdown, respectively, with the greatest changes at the center of lesions.<sup>41</sup> Recently, a hyperintense cortical signal seen on MRI scan in non-enhanced T1-weighted cortex images has been associated with seizures complicating inflammatory PML.<sup>37</sup>

In most cases of PML, the combined clinical and radiographic presentations support a presumptive diagnosis. Confirming the diagnosis, however, is invaluable. Certainly for atypical cases but even for typical cases, confirmation allows physicians to initiate ART rapidly and with certainty and prevents the need to revisit the diagnosis when disease progression continues. Confirmed diagnosis also informs discussions of prognosis.

The usual first step in confirming the diagnosis is to test cerebrospinal fluid (CSF) by polymerase chain reaction (PCR) for the presence of JCV DNA. The assay is positive in approximately 70% to 90% of patients not taking ART, for whom a positive result can be considered diagnostic in the appropriate clinical context, namely, subacute onset of focal neurological abnormalities and suggestive imaging findings.<sup>9,42</sup> JCV may be detectable in the CSF of as few as 60% of ART-treated patients.<sup>43</sup> In patients not taking ART, the number of JCV DNA copies can add additional information for prognosis, although the relationship between copy number and prognosis is less clear in patients taking ART.<sup>44,45</sup> CSF analysis can be repeated if JCV PCR is negative yet suspicion of PML remains high and alternative diagnoses have been excluded (e.g., by PCR analyses of CSF for varicella zoster virus and Epstein-Barr virus for varicella zoster virus encephalitis and primary CNS lymphoma, respectively). Because JCV DNA viral load in CSF may be very low even with active PML, highly sensitive PCR performance is desirable. Sensitive assays that detect as few as 50 copies/ml are now available, with some research labs exceeding this level of sensitivity., detection of JCV virus in CSF in any amount with the appropriate clinical and imaging findings strongly supports the diagnosis of PML.<sup>46</sup> Analysis of plasma samples for detection of JCV by PCR when positive are relatively specific for PML (~92% in HIV patients), while the sensitivity is less than 40% in this setting.<sup>47</sup>

In some instances, brain biopsy is required to establish the diagnosis. PML can usually be identified by the characteristic tissue cytopathology, including oligodendrocytes with intranuclear inclusions, bizarre astrocytes, and lipid-laden macrophages, with identification of JCV or cross reacting polyoma virus by immunohistochemistry, in situ nucleic acid hybridization, or electron microscopy.<sup>12,48,49</sup>

Serologic testing is generally not useful because of high anti-JCV seroprevalence in the general population. Recently, however, antibody testing has been assessed for stratifying risk of PML with natalizumab treatment.<sup>6</sup> Significant increases in JC virus specific antibody titers<sup>50</sup> and detection of intrathecally produced anti-JCV antibodies may prove useful for diagnostic testing<sup>51</sup> but requires further prospective study.

## Preventing Exposure

JCV has a worldwide distribution and, as previously noted, 20% to 60% of people exhibit serologic evidence of exposure by their late teens.<sup>52</sup> Currently, there is no known way to prevent exposure to the virus.

## Preventing Disease

In many individuals, JCV infection is likely latent and intermittently productive, although clinically silent, in the kidney or other systemic sites. Systemic infection may increase in the presence of immunosuppression. It remains a subject of debate whether JCV infection is also latent in the CNS or whether PML results from hematogenous dissemination of infection to the brain resulting in subsequent PML lesion development within months of entry to CNS.<sup>53,54</sup> Protection is conferred by either preventing spread to the CNS or by preventing active viral replication with effective immunosurveillance. Therefore, the only effective way to prevent disease is to prevent progression of HIV-related immunosuppression with ART (**AII**).

## Treating Disease

No specific therapy exists for JCV infection or PML. The main approach to treatment involves ART to reverse the immunosuppression that interferes with the normal host response to this virus. In patients with PML who are not on therapy, ART should be started immediately (**AII**). In this setting, more than half of HIV-infected PML patients experience a remission in which disease progression stops. Neurological deficits often persist, but some patients experience clinical improvement.<sup>28,29,55-60</sup> In one retrospective study of 118 consecutive patients with PML who received ART, 75 patients (63.6%) survived for a median of 114 weeks (2.2 years) after diagnosis of PML.<sup>60</sup> Neurological function in the survivors was categorized as cure or improvement in 33, stabilization or worsening in 40, and unknown in 2. Another retrospective case series reported that 42% of PML survivors on ART had moderate-to-severe disability.<sup>61</sup> Peripheral blood CD4 cell count at presentation was the only variable that predicted survival; the odds ratio for death was 2.7 among patients with CD4 counts <100 cells/mm<sup>3</sup> compared with patients who had higher CD4 cell counts. In other case series, worse prognosis was also associated with high plasma HIV RNA levels at the time of presentation, poor virologic responses to ART, and the presence of lesions in the brain stem.<sup>29,32,56,57,59,60,62</sup> Contrast enhancement on imaging may predict better outcome, as it is indicative of an immune response to the virus.<sup>31</sup> In PML occurring in multiple sclerosis patients, younger age, more restricted unilobar disease, and lower CSF JCV DNA copy numbers are associated with better outcomes.<sup>63</sup>

ART should be optimized for HIV virologic suppression in patients with PML who have received ART but remain viremic because of inadequate adherence or ARV resistance (**AIII**). More problematic are patients who develop PML despite successful HIV virologic suppression while taking ART. A preliminary report of PML patients treated intensively with four classes of ART (including enfuvirtide) suggested that the strategy might offer higher than anticipated survival,<sup>64</sup> but it has not yet been followed by a full report or structured trial. Therefore, there is no evidence supporting ART intensification for PML.

The use of ARV drugs that better penetrate the CNS also has been proposed, with use of the CNS Penetration Effectiveness (CPE) score of drug regimens as a guide. This score is based on the pharmacology of ARV drugs with respect to their chemical characteristics as well as demonstrated entry into the CNS (or, more often, the CSF) and, where available, on their CNS anti-HIV activity.<sup>65</sup> One report found that at the beginning of the combination ART era, a high CPE score was associated with longer survival after a PML diagnosis, whereas in the late, more recent ART period, the effect of the CPE score disappeared as more potent ARV regimens led to more effective plasma viral load control.<sup>66</sup> Hence, in the current era, the effectiveness of selecting a treatment regimen with a high CPE score is not established. It seems likely that systemic rather than CNS efficacy is the salient aspect of ART in this setting because ART's most important effect on PML may be restoration of effective anti-JCV immunity that can limit CNS infection.<sup>67,68</sup>

The history of more specifically targeted treatments for PML includes many anecdotal reports of success

that have not been confirmed by controlled studies. Based on case reports and demonstration of *in vitro* inhibitory activity against JCV, intravenous (IV) and intrathecal cytarabine (cytosine arabinoside) were tested in a clinical trial, but neither demonstrated clinical benefit.<sup>69</sup> Therefore, treatment with cytarabine **is not recommended** (AII). Similarly, cidofovir initially was reported to have a salutary clinical effect, but several large studies—including retrospective case-control studies, an open-label clinical trial, and a meta-analysis that included patients from five large studies—demonstrated no benefit.<sup>43,58-60,70</sup> Thus, treatment with cidofovir is also **not recommended** (AII). A lipid-ester derivative, hexadecyloxypropyl-cidofovir, recently has been reported to suppress JCV replication in cell culture,<sup>71</sup> but its efficacy in HIV-associated PML is unknown.

On the basis of a report indicating that the serotonergic 5HT2a receptor can serve as a cellular receptor for JCV in a glial cell culture system,<sup>72,73</sup> drugs that block the 5HT2a receptor, including olanzapine, zispradone, mirtazapine, cyproheptadine, and risperidone, have been suggested as treatment for PML,<sup>74</sup> although the rationale for this practice has been questioned.<sup>75</sup> Again, anecdotes about favorable outcomes<sup>1,76-79</sup> have not been substantiated by reports of genuine benefit in larger case series, cohort studies, or formal clinical trials. Thus, at this time, treatment with this class of drugs **is not recommended** (BIII).

After a cell-culture study indicated that JCV replication could be inhibited by a topoisomerase inhibitor,<sup>80</sup> an analogue, topotecan, was studied in a small trial. Results suggested a salutary effect in some patients, although the outcome likely was little different from the natural course in other patients with AIDS, and the main toxicities were hematologic.<sup>81</sup> At this time, topotecan also **is not recommended** (BIII).

A Phase I/II clinical trial of the antimalarial drug mefloquine was initiated based on its demonstrated *in vitro* anti-JCV activity. The trial was later halted by the sponsor, because demonstration of efficacy was futile.<sup>82</sup> Mefloquine **cannot be recommended**.

Immunomodulatory approaches to the treatment of PML in HIV-infected patients have also been tried, but none has yet been studied in a prospective, controlled clinical trial. Although an initial retrospective analysis suggested that interferon-alpha might improve survival,<sup>83</sup> a subsequent retrospective analysis did not demonstrate benefit beyond that afforded by ART; therefore, interferon-alpha **is not recommended** (BIII).<sup>84</sup> A single report described failure of interferon-beta treatment of HIV-associated PML<sup>85</sup> and natalizumab-related PML developed in patients given interferon-beta for multiple sclerosis.<sup>15</sup> Case reports have described improvement or recovery in PML-related neurological dysfunction in three patients who were not HIV infected and were treated with IL-2: one with Hodgkin lymphoma treated with autologous bone marrow transplantation, one with low-grade lymphoma and allogeneic stem cell transplantation, and one with myelodysplastic syndrome.<sup>86-88</sup> Like the other reports, these too have not been followed up with more substantial trials. Recent interest in recombinant IL-7 for treatment of PML when CD4 lymphopenia is persistent, sometimes in combination with VP-1 vaccination strategy, are under consideration as an alternative adjuvant immune therapy to improve PML outcomes.<sup>89-93</sup>

### ***Special Considerations with Regard to Starting ART***

ART should be started in patients not on HIV treatment as soon as PML is recognized (AII). For patients already on treatment who have demonstrated plasma HIV viremia and are adherent to therapy, ART should be adjusted based on plasma virus susceptibility (AII).

### ***Monitoring of Response to Therapy and Adverse Events (Including IRIS)***

Treatment response should be monitored with clinical examination and MRI. In patients with detectable JCV DNA in their CSF before initiation of ARV treatment, quantitation of CSF JCV DNA may prove useful as an index to follow for assessing treatment response. No clear guidelines exist for the timing of follow-up assessments, but it is reasonable to be guided by clinical progress. Often clinical deterioration is seen before stabilization and improvement occurs.<sup>94</sup> In patients who appear stable or improved, neuroimaging can be obtained 6 to 8 weeks after ART initiation to screen for radiographic signs of progression or of immune response, and can serve as a further baseline for subsequent scans should the patient begin to deteriorate.



In patients who clinically worsen before or after this 6- to 8-week period, repeat neuroimaging should be obtained as soon as worsening is recognized **(BIII)**.

### ***PML-Immune Reconstitution Inflammatory Syndrome***

PML has been reported to occur within the first weeks to months after initiating ART<sup>2,32,33,95-97</sup> with clinical and radiographic features that differ from classical PML, including lesions with contrast enhancement, edema and mass effect, and a more rapid clinical course.<sup>98,99</sup> As with other presentations of IRIS, it is more likely after advanced HIV with low CD4 counts, and with greater decline in HIV viral load on initiation of ARV. This presentation has been referred to as inflammatory PML or PML-immune reconstitution inflammatory syndrome (PML-IRIS). Both unmasking of cryptic PML and paradoxical worsening in a patient with an established PML diagnosis have been observed. Histopathology typically demonstrates perivascular mononuclear inflammatory infiltration.<sup>100-103</sup> Unmasked PML-IRIS is presumed to represent the effects of a restored immune response to JCV infection in the context of ART, with resultant local immune and inflammatory responses, but other undefined factors also may contribute to unmasked PML-IRIS.

Because ART-induced immune reconstitution may be associated with both onset and paradoxical worsening of PML, corticosteroids have been used empirically in this setting, with reported benefit.<sup>2,96,104</sup> Further study of corticosteroids for treatment of PML-IRIS is needed to confirm efficacy and refine dosage and duration. At present, however, use of corticosteroids to treat of PML-IRIS appears justified characterized by contrast enhancement, edema or mass effect, and clinical deterioration **(BIII)**. The decision to use steroids can be difficult because it is the immune response to JCV that controls the infection and treatments that blunt that response can be deleterious. Nevertheless, the inflammatory response against PML can, at times, be more damaging than the virus itself, and corticosteroids appear to have a role in treatment of these patients.

The dosage and duration of corticosteroids for PML-IRIS have not been established. In the absence of comparative data, adjuvant corticosteroid therapy should be tailored to individual patients. One approach, modeled on treatment of multiple sclerosis flairs, is to begin with a 3- to 5 day course of IV methylprednisolone dosed at 1 g per day, followed by an oral prednisone taper, dosed according to clinical response. A taper may begin with a dose of 60 mg per day in a single dose, tapered over 1 to 6 weeks. Clinical status should be monitored carefully during this taper in an attempt to minimize systemic and immune effects while avoiding IRIS recrudescence. Contrast-enhanced MRI at 2 to 6 weeks may be helpful in documenting resolution of inflammation and edema and to obtain a new baseline, recognizing that the MRI appearance may worsen despite clinical improvement and that clinical status is likely the best indicator of treatment efficacy. Importantly, ART should be continued at the standard therapeutic doses during this period **(AIII)**.

Several case reports suggest that maraviroc might be beneficial for PML-IRIS,<sup>105</sup> presumably related to the immunomodulatory rather than ARV properties of the CCR5 inhibitor. However, no comparative studies in HIV-associated PML have confirmed benefit of inclusion of maraviroc in HIV therapy in this setting.<sup>105-108</sup>

Although some clinicians may want to use adjuvant corticosteroid therapy to treat all cases of PML regardless of whether there is evidence of IRIS, this action is not justified and should be discouraged in patients who have no evidence of substantial inflammation on contrast-enhanced neuroimaging or on pathological examination **(CIII)**. In patients whose condition worsens, imaging can be repeated to monitor for development of IRIS before initiating corticosteroids.

### ***Managing Treatment Failure***

PML remission can take several weeks and there are no strict criteria to define treatment failure. However, a working definition may be continued clinical worsening and continued detection of CSF JCV without substantial decrease within 3 months of initiating of ART. Changes in plasma HIV RNA levels and blood CD4 cell count responses provide ancillary predictive information. Failing ART regimens should be changed based on standard guidelines for the use of ART. When PML continues to worsen despite fully suppressive anti-HIV treatment, one of the unproven therapies described above can be considered, although the possibility of toxicity must be balanced against the unproven benefits of these treatments.

## Preventing Recurrence

Patients who experience remission of PML after ART rarely suffer subsequent recrudescence.<sup>58,109</sup> The main preventive measure, based on its role in reversing the disease, is treatment with an effective ART regimen that suppresses viremia and maintains CD4 cell counts **(AII)**.

## Special Considerations During Pregnancy

Diagnostic evaluation of PML should be the same in pregnant women as in women who are not pregnant. Therapy during pregnancy should consist of initiating or optimizing the ARV regimen. If corticosteroid therapy is initiated during pregnancy, blood sugar monitoring should be included as insulin resistance is increased during pregnancy.

## Recommendations for Preventing and Treating PML and JCV

- There is no effective antiviral therapy for preventing or treating JCV infections or PML.
- The main approach to treatment is to preserve immune function and reverse HIV-associated immunosuppression with effective ART.
- HIV-associated PML is often complicated by clinically significant IRIS that may require administration of corticosteroid therapy.
- In ART-naïve patients who are diagnosed with PML, ART should be started immediately **(AII)**.
- In patients who are receiving ART but remain viremic because of inadequate adherence or drug resistance, ART should be optimized to achieve HIV suppression **(AIII)**.

**Key to Acronyms:** ART = antiretroviral therapy; JCV = JC virus; PML = progressive multifocal leukoencephalopathy.

## References

1. Koralnik IJ. Progressive multifocal leukoencephalopathy revisited: Has the disease outgrown its name? *Ann Neurol*. 2006;60(2):162-173. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16862584>.
2. Cinque P, Koralnik IJ, Gerevini S, Miro JM, Price RW. Progressive multifocal leukoencephalopathy in HIV-1 infection. *Lancet Infect Dis*. 2009;9(10):625-636. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19778765>.
3. Kean JM, Rao S, Wang M, Garcea RL. Seroepidemiology of human polyomaviruses. *PLoS Pathog*. 2009;5(3):e1000363. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19325891>.
4. Egli A, Infanti L, Dumoulin A, et al. Prevalence of polyomavirus BK and JC infection and replication in 400 healthy blood donors. *J Infect Dis*. 2009;199(6):837-846. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19434930>.
5. Antonsson A, Green AC, Mallitt KA, et al. Prevalence and stability of antibodies to the BK and JC polyomaviruses: a long-term longitudinal study of Australians. *J Gen Virol*. 2010;91(Pt 7):1849-1853. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20219899>.
6. Gorelik L, Lerner M, Bixler S, et al. Anti-JC virus antibodies: implications for PML risk stratification. *Ann Neurol*. 2010;68(3):295-303. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20737510>.
7. Kitamura T, Aso Y, Kuniyoshi N, Hara K, Yogo Y. High incidence of urinary JC virus excretion in nonimmunosuppressed older patients. *J Infect Dis*. 1990;161(6):1128-1133. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/2161040>.
8. Sundsfjord A, Flaegstad T, Flo R, et al. BK and JC viruses in human immunodeficiency virus type 1-infected persons: prevalence, excretion, viremia, and viral regulatory regions. *J Infect Dis*. 1994;169(3):485-490. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/8158020>.
9. Koralnik IJ, Boden D, Mai VX, Lord CI, Letvin NL. JC virus DNA load in patients with and without progressive multifocal leukoencephalopathy. *Neurology*. 1999;52(2):253-260. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/9932940>.
10. Lednicky JA, Vilchez RA, Keitel WA, et al. Polyomavirus JCV excretion and genotype analysis in HIV-infected patients receiving highly active antiretroviral therapy. *AIDS*. 2003;17(6):801-807. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/12660526>.

11. Kato A, Kitamura T, Takasaka T, et al. Detection of the archetypal regulatory region of JC virus from the tonsil tissue of patients with tonsillitis and tonsillar hypertrophy. *J Neurovirol.* 2004;10(4):244-249. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15371154>.
12. Richardson EP, Jr., Webster HD. Progressive multifocal leukoencephalopathy: its pathological features. *Prog Clin Biol Res.* 1983;105:191-203. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/6304757>.
13. Garcia-Suarez J, de Miguel D, Krsnik I, Banas H, Arribas I, Burgaleta C. Changes in the natural history of progressive multifocal leukoencephalopathy in HIV-negative lymphoproliferative disorders: impact of novel therapies. *Am J Hematol.* 2005;80(4):271-281. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16315252>.
14. Amend KL, Turnbull B, Foskett N, Napalkov P, Kurth T, Seeger J. Incidence of progressive multifocal leukoencephalopathy in patients without HIV. *Neurology.* 2010;75(15):1326-1332. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20938025>.
15. Clifford DB, De Luca A, Simpson DM, Arendt G, Giovannoni G, Nath A. Natalizumab-associated progressive multifocal leukoencephalopathy in patients with multiple sclerosis: lessons from 28 cases. *Lancet Neurol.* 2010;9(4):438-446. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20298967>.
16. Molloy ES, Calabrese LH. Therapy: Targeted but not trouble-free: efalizumab and PML. *Nat Rev Rheumatol.* 2009;5(8):418-419. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19648939>.
17. Kumar D, Bouldin TW, Berger RG. A case of progressive multifocal leukoencephalopathy in a patient treated with infliximab. *Arthritis Rheum.* 2010;62(11):3191-3195. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20722036>.
18. Carson KR, Focosi D, Major EO, et al. Monoclonal antibody-associated progressive multifocal leukoencephalopathy in patients treated with rituximab, natalizumab, and efalizumab: a Review from the Research on Adverse Drug Events and Reports (RADAR) Project. *Lancet Oncol.* 2009;10(8):816-824. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19647202>.
19. Boue F, Gabarre J, Gisselbrecht C, et al. Phase II trial of CHOP plus rituximab in patients with HIV-associated non-Hodgkin's lymphoma. *J Clin Oncol.* 2006;24(25):4123-4128. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16896005>.
20. Mounier N, Spina M, Gisselbrecht C. Modern management of non-Hodgkin lymphoma in HIV-infected patients. *Br J Haematol.* 2007;136(5):685-698. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17229246>.
21. Mateen FJ, Muralidharan R, Carone M, et al. Progressive multifocal leukoencephalopathy in transplant recipients. *Ann Neurol.* 2011;70(2):305-322. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21823157>.
22. Petit CK, Cho ES, Lemann W, Navia BA, Price RW. Neuropathology of acquired immunodeficiency syndrome (AIDS): an autopsy review. *J Neuropathol Exp Neurol.* 1986;45(6):635-646. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/3021914>.
23. Anders KH, Guerra WF, Tomiyasu U, Verity MA, Vinters HV. The neuropathology of AIDS. UCLA experience and review. *Am J Pathol.* 1986;124(3):537-558. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/2876640>.
24. Lang W, Miklossy J, Deruaz JP, et al. Neuropathology of the acquired immune deficiency syndrome (AIDS): a report of 135 consecutive autopsy cases from Switzerland. *Acta Neuropathol.* 1989;77(4):379-390. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/2540610>.
25. Berger JR, Mucke L. Prolonged survival and partial recovery in AIDS-associated progressive multifocal leukoencephalopathy. *Neurology.* 1988;38(7):1060-1065. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/3386823>.
26. d'Arminio Monforte A, Cinque P, Mocroft A, et al. Changing incidence of central nervous system diseases in the EuroSIDA cohort. *Ann Neurol.* 2004;55(3):320-328. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/14991809>.
27. Casado JL, Corral I, Garcia J, et al. Continued declining incidence and improved survival of progressive multifocal leukoencephalopathy in HIV/AIDS patients in the current era. *Eur J Clin Microbiol Infect Dis.* 2014;33(2):179-187. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23948752>.
28. Clifford DB, Yiannoutsos C, Glicksman M, et al. HAART improves prognosis in HIV-associated progressive multifocal leukoencephalopathy. *Neurology.* 1999;52(3):623-625. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/10025799>.
29. Antinori A, Cingolani A, Lorenzini P, et al. Clinical epidemiology and survival of progressive multifocal leukoencephalopathy in the era of highly active antiretroviral therapy: data from the Italian Registry Investigative Neuro AIDS (IRINA). *J Neurovirol.* 2003;9 Suppl 1:47-53. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/12709872>.



30. Melliez H, Mary-Krause M, Bocket L, et al. Risk of Progressive Multifocal Leukoencephalopathy in the Combination Antiretroviral Therapy Era in the French Hospital Database on Human Immunodeficiency Virus (ANRS-C4). *Clin Infect Dis*. 2018;67(2):275-282. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29635465>.
31. Berger JR, Levy RM, Flomenhoft D, Dobbs M. Predictive factors for prolonged survival in acquired immunodeficiency syndrome-associated progressive multifocal leukoencephalopathy. *Ann Neurol*. 1998;44(3):341-349. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/9749600>.
32. Cinque P, Bossolasco S, Brambilla AM, et al. The effect of highly active antiretroviral therapy-induced immune reconstitution on development and outcome of progressive multifocal leukoencephalopathy: study of 43 cases with review of the literature. *J Neurovirol*. 2003;9 Suppl 1:73-80. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/12709876>.
33. Du Pasquier RA, Koralnik IJ. Inflammatory reaction in progressive multifocal leukoencephalopathy: harmful or beneficial? *J Neurovirol*. 2003;9 Suppl 1:25-31. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/12709868>.
34. Bernal-Cano F, Joseph JT, Koralnik IJ. Spinal cord lesions of progressive multifocal leukoencephalopathy in an acquired immunodeficiency syndrome patient. *J Neurovirol*. 2007;13(5):474-476. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17994433>.
35. Zunt JR, Tu RK, Anderson DM, Copass MC, Marra CM. Progressive multifocal leukoencephalopathy presenting as human immunodeficiency virus type 1 (HIV)-associated dementia. *Neurology*. 1997;49(1):263-265. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/9222204>.
36. Lima MA, Drislane FW, Koralnik IJ. Seizures and their outcome in progressive multifocal leukoencephalopathy. *Neurology*. 2006;66(2):262-264. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16434670>.
37. Khoury MN, Alsop DC, Agnihotri SP, et al. Hyperintense cortical signal on magnetic resonance imaging reflects focal leukocortical encephalitis and seizure risk in progressive multifocal leukoencephalopathy. *Ann Neurol*. 2014;75(5):659-669. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24752885>.
38. Chang L, Ernst T, Tornatore C, et al. Metabolite abnormalities in progressive multifocal leukoencephalopathy by proton magnetic resonance spectroscopy. *Neurology*. 1997;48(4):836-845. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/9109865>.
39. Mader I, Herrlinger U, Klose U, Schmidt F, Kuker W. Progressive multifocal leukoencephalopathy: analysis of lesion development with diffusion-weighted MRI. *Neuroradiology*. 2003;45(10):717-721. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/12942223>.
40. da Pozzo S, Manara R, Tonello S, Carollo C. Conventional and diffusion-weighted MRI in progressive multifocal leukoencephalopathy: new elements for identification and follow-up. *Radiol Med*. 2006;111(7):971-977. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17021685>.
41. Shah R, Bag AK, Chapman PR, Cure JK. Imaging manifestations of progressive multifocal leukoencephalopathy. *Clin Radiol*. 2010;65(6):431-439. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20451009>.
42. Cinque P, Scarpellini P, Vago L, Linde A, Lazzarin A. Diagnosis of central nervous system complications in HIV-infected patients: cerebrospinal fluid analysis by the polymerase chain reaction. *AIDS*. 1997;11(1):1-17. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/9110070>.
43. De Luca A, Ammassari A, Pezzotti P, et al. Cidofovir in addition to antiretroviral treatment is not effective for AIDS-associated progressive multifocal leukoencephalopathy: a multicohort analysis. *AIDS*. 2008;22(14):1759-1767. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18753934>.
44. Yiannoutsos CT, Major EO, Curfman B, et al. Relation of JC virus DNA in the cerebrospinal fluid to survival in acquired immunodeficiency syndrome patients with biopsy-proven progressive multifocal leukoencephalopathy. *Ann Neurol*. 1999;45(6):816-821. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/10360779>.
45. Bossolasco S, Calori G, Moretti F, et al. Prognostic significance of JC virus DNA levels in cerebrospinal fluid of patients with HIV-associated progressive multifocal leukoencephalopathy. *Clin Infect Dis*. 2005;40(5):738-744. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15714422>.
46. Berger JR, Aksamit AJ, Clifford DB, et al. PML diagnostic criteria: consensus statement from the AAN Neuroinfectious Disease Section. *Neurology*. 2013;80(15):1430-1438. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23568998>.
47. Ferretti F, Bestetti A, Yiannoutsos CT, et al. Diagnostic and Prognostic Value of JC Virus DNA in Plasma in Progressive Multifocal Leukoencephalopathy. *Clin Infect Dis*. 2018;67(1):65-72. Available at: <https://www.ncbi.nlm.nih.gov/>

[pubmed/29346632](https://pubmed/29346632).

48. Silver SA, Arthur RR, Erozan YS, Sherman ME, McArthur JC, Uematsu S. Diagnosis of progressive multifocal leukoencephalopathy by stereotactic brain biopsy utilizing immunohistochemistry and the polymerase chain reaction. *Acta Cytol.* 1995;39(1):35-44. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/7847007>.
49. Jochum W, Weber T, Frye S, Hunsmann G, Luke W, Aguzzi A. Detection of JC virus by anti-VP1 immunohistochemistry in brains with progressive multifocal leukoencephalopathy. *Acta Neuropathol.* 1997;94(3):226-231. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/9292691>.
50. Viscidi RP, Khanna N, Tan CS, et al. JC virus antibody and viremia as predictors of progressive multifocal leukoencephalopathy in human immunodeficiency virus-1-infected individuals. *Clin Infect Dis.* 2011;53(7):711-715. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21852452>.
51. Knowles WA, Luxton RW, Hand JF, Gardner SD, Brown DW. The JC virus antibody response in serum and cerebrospinal fluid in progressive multifocal leukoencephalopathy. *Clin Diagn Virol.* 1995;4(2):183-194. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15566839>.
52. Knowles WA. Discovery and epidemiology of the human polyomaviruses BK virus (BKV) and JC virus (JCV). *Adv Exp Med Biol.* 2006;577:19-45. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16626025>.
53. Perez-Liz G, Del Valle L, Gentilella A, Croul S, Khalili K. Detection of JC virus DNA fragments but not proteins in normal brain tissue. *Ann Neurol.* 2008;64(4):379-387. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18688812>.
54. Tan CS, Ellis LC, Wuthrich C, et al. JC virus latency in the brain and extraneural organs of patients with and without progressive multifocal leukoencephalopathy. *J Virol.* 2010;84(18):9200-9209. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20610709>.
55. Dworkin MS, Wan PC, Hanson DL, Jones JL. Progressive multifocal leukoencephalopathy: improved survival of human immunodeficiency virus-infected patients in the protease inhibitor era. *J Infect Dis.* 1999;180(3):621-625. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/10438348>.
56. Gasnault J, Taoufik Y, Goujard C, et al. Prolonged survival without neurological improvement in patients with AIDS-related progressive multifocal leukoencephalopathy on potent combined antiretroviral therapy. *J Neurovirol.* 1999;5(4):421-429. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/10463864>.
57. Tassie JM, Gasnault J, Bentata M, et al. Survival improvement of AIDS-related progressive multifocal leukoencephalopathy in the era of protease inhibitors. Clinical Epidemiology Group. French Hospital Database on HIV. *AIDS.* 1999;13(14):1881-1887. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/10513646>.
58. Cinque P, Pierotti C, Vigano MG, et al. The good and evil of HAART in HIV-related progressive multifocal leukoencephalopathy. *J Neurovirol.* 2001;7(4):358-363. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/11517417>.
59. Marra CM, Rajcic N, Barker DE, et al. A pilot study of cidofovir for progressive multifocal leukoencephalopathy in AIDS. *AIDS.* 2002;16(13):1791-1797. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/12218391>.
60. Berenguer J, Miralles P, Arrizabalaga J, et al. Clinical course and prognostic factors of progressive multifocal leukoencephalopathy in patients treated with highly active antiretroviral therapy. *Clin Infect Dis.* 2003;36(8):1047-1052. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/12684918>.
61. Lima MA, Bernal-Cano F, Clifford DB, Gandhi RT, Koralnik IJ. Clinical outcome of long-term survivors of progressive multifocal leukoencephalopathy. *J Neurol Neurosurg Psychiatry.* 2010;81(11):1288-1291. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20710013>.
62. Pazzi AL, Galli M, et al. The relationship between outcome of progressive multifocal leukoencephalopathy and type and response to ART in previously HAART-untreated patients. Presented at: 14th Conference on Retroviruses and Opportunistic Infections; 2007; Los Angeles, CA.
63. Dong-Si T, Gheuens S, Gangadharan A, et al. Predictors of survival and functional outcomes in natalizumab-associated progressive multifocal leukoencephalopathy. *J Neurovirol.* 2015;21(6):637-644. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25771865>.
64. Gasnault J, Hendel-Chavez H, et al. Acceleration of immune recovery on intensified ART improves survival in patients with AIDS-related PML: preliminary reports of the ANRS 125 trial. Presented at: 14th Conference on Retroviruses and Opportunistic Infections; 2007; Los Angeles, CA.
65. Letendre S, Marquie-Beck J, Capparelli E, et al. Validation of the CNS Penetration-Effectiveness rank for quantifying

- antiretroviral penetration into the central nervous system. *Arch Neurol*. 2008;65(1):65-70. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18195140>.
66. Lanoy E, Guiguet M, Bentata M, et al. Survival after neuroAIDS: association with antiretroviral CNS Penetration-Effectiveness score. *Neurology*. 2011;76(7):644-651. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21248274>.
  67. Garvey L, Winston A, Walsh J, et al. Antiretroviral therapy CNS penetration and HIV-1-associated CNS disease. *Neurology*. 2011;76(8):693-700. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21339496>.
  68. Fanjul F, Riveiro-Barciela M, Gonzalez J, et al. Evaluation of progressive multifocal leukoencephalopathy treatments in a Spanish cohort of HIV-infected patients: do protease inhibitors improve survival regardless of central nervous system penetration-effectiveness (CPE) score? *HIV Med*. 2013;14(5):321-325. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23217049>.
  69. Hall CD, Dafni U, Simpson D, et al. Failure of cytarabine in progressive multifocal leukoencephalopathy associated with human immunodeficiency virus infection. AIDS Clinical Trials Group 243 Team. *N Engl J Med*. 1998;338(19):1345-1351. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/9571254>.
  70. Gasnault J, Kousignian P, Kahraman M, et al. Cidofovir in AIDS-associated progressive multifocal leukoencephalopathy: a monocenter observational study with clinical and JC virus load monitoring. *J Neurovirol*. 2001;7(4):375-381. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/11517420>.
  71. Jiang ZG, Cohen J, Marshall LJ, Major EO. Hexadecyloxypropyl-cidofovir (CMX001) suppresses JC virus replication in human fetal brain SVG cell cultures. *Antimicrob Agents Chemother*. 2010;54(11):4723-4732. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20823288>.
  72. Elphick GF, Querbes W, Jordan JA, et al. The human polyomavirus, JCV, uses serotonin receptors to infect cells. *Science*. 2004;306(5700):1380-1383. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15550673>.
  73. O'Hara BA, Atwood WJ. Interferon beta1-a and selective anti-5HT(2a) receptor antagonists inhibit infection of human glial cells by JC virus. *Virus Res*. 2008;132(1-2):97-103. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18093678>.
  74. Altschuler EL, Kast RE. The atypical antipsychotic agents ziprasidone [correction of zisprasidone], risperidone and olanzapine as treatment for and prophylaxis against progressive multifocal leukoencephalopathy. *Med Hypotheses*. 2005;65(3):585-586. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16004936>.
  75. Santagata S, Kinney HC. Mechanism of JCV entry into oligodendrocytes. *Science*. 2005;309(5733):381-382. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16020715>.
  76. Focosi D, Fazzi R, Montanaro D, Emdin M, Petrini M. Progressive multifocal leukoencephalopathy in a haploidentical stem cell transplant recipient: a clinical, neuroradiological and virological response after treatment with risperidone. *Antiviral Res*. 2007;74(2):156-158. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17140673>.
  77. Vulliemoz S, Lurati-Ruiz F, Borruat FX, et al. Favourable outcome of progressive multifocal leukoencephalopathy in two patients with dermatomyositis. *J Neurol Neurosurg Psychiatry*. 2006;77(9):1079-1082. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16914758>.
  78. Lanza fame M, Ferrari S, Lattuada E, et al. Mirtazapine in an HIV-1 infected patient with progressive multifocal leukoencephalopathy. *Infez Med*. 2009;17(1):35-37. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19359824>.
  79. Cettomai D, McArthur JC. Mirtazapine use in human immunodeficiency virus-infected patients with progressive multifocal leukoencephalopathy. *Arch Neurol*. 2009;66(2):255-258. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19204164>.
  80. Kerr DA, Chang CF, Gordon J, Bjornsti MA, Khalili K. Inhibition of human neurotropic virus (JCV) DNA replication in glial cells by camptothecin. *Virology*. 1993;196(2):612-618. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/8396804>.
  81. Royal W, 3rd, Dupont B, McGuire D, et al. Topotecan in the treatment of acquired immunodeficiency syndrome-related progressive multifocal leukoencephalopathy. *J Neurovirol*. 2003;9(3):411-419. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/12775425>.
  82. Clifford DB, Nath A, Cinque P, et al. A study of mefloquine treatment for progressive multifocal leukoencephalopathy: results and exploration of predictors of PML outcomes. *J Neurovirol*. 2013;19(4):351-358. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23733308>.
  83. Huang SS, Skolasky RL, Dal Pan GJ, Royal W, 3rd, McArthur JC. Survival prolongation in HIV-associated progressive



multifocal leukoencephalopathy treated with alpha-interferon: an observational study. *J Neurovirol*. 1998;4(3):324-332. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/9639075>.

84. Geschwind MD, Skolasky RI, Royal WS, McArthur JC. The relative contributions of HAART and alpha-interferon for therapy of progressive multifocal leukoencephalopathy in AIDS. *J Neurovirol*. 2001;7(4):353-357. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/11517416>.
85. Nath A, Venkataramana A, Reich DS, Cortese I, Major EO. Progression of progressive multifocal leukoencephalopathy despite treatment with beta-interferon. *Neurology*. 2006;66(1):149-150. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16401874>.
86. Przepiorka D, Jaeckle KA, Birdwell RR, et al. Successful treatment of progressive multifocal leukoencephalopathy with low-dose interleukin-2. *Bone Marrow Transplant*. 1997;20(11):983-987. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/9422479>.
87. Buckanovich RJ, Liu G, Stricker C, et al. Nonmyeloablative allogeneic stem cell transplantation for refractory Hodgkin's lymphoma complicated by interleukin-2 responsive progressive multifocal leukoencephalopathy. *Ann Hematol*. 2002;81(7):410-413. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/12185517>.
88. Kunschner L, Scott TF. Sustained recovery of progressive multifocal leukoencephalopathy after treatment with IL-2. *Neurology*. 2005;65(9):1510. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16275856>.
89. Sospedra M, Schippling S, Yousef S, et al. Treating progressive multifocal leukoencephalopathy with interleukin 7 and vaccination with JC virus capsid protein VP1. *Clin Infect Dis*. 2014;59(11):1588-1592. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25214510>.
90. Pavlovic D, Patera AC, Nyberg F, Gerber M, Liu M, Progressive Multifocal Leukoencephalopathy C. Progressive multifocal leukoencephalopathy: current treatment options and future perspectives. *Ther Adv Neurol Disord*. 2015;8(6):255-273. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26600871>.
91. Soleimani-Meigooni DN, Schwetye KE, Angeles MR, et al. JC virus granule cell neuronopathy in the setting of chronic lymphopenia treated with recombinant interleukin-7. *J Neurovirol*. 2017;23(1):141-146. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27421731>.
92. Miskin DP, Chalkias SG, Dang X, Bord E, Batson S, Koralnik IJ. Interleukin-7 treatment of PML in a patient with idiopathic lymphocytopenia. *Neurol Neuroimmunol Neuroinflamm*. 2016;3(2):e213. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27144212>.
93. Ray U, Cinque P, Gerevini S, et al. JC polyomavirus mutants escape antibody-mediated neutralization. *Sci Transl Med*. 2015;7(306):306ra151. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26400912>.
94. Gasnault J, Costagliola D, Hendel-Chavez H, et al. Improved survival of HIV-1-infected patients with progressive multifocal leukoencephalopathy receiving early 5-drug combination antiretroviral therapy. *PLoS One*. 2011;6(6):e20967. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21738597>.
95. Vendrely A, Bienvenu B, Gasnault J, Thiebault JB, Salmon D, Gray F. Fulminant inflammatory leukoencephalopathy associated with HAART-induced immune restoration in AIDS-related progressive multifocal leukoencephalopathy. *Acta Neuropathol*. 2005;109(4):449-455. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15739098>.
96. Tan K, Roda R, Ostrow L, McArthur J, Nath A. PML-IRIS in patients with HIV infection: clinical manifestations and treatment with steroids. *Neurology*. 2009;72(17):1458-1464. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19129505>.
97. Sainz-de-la-Maza S, Casado JL, Perez-Elias MJ, et al. Incidence and prognosis of immune reconstitution inflammatory syndrome in HIV-associated progressive multifocal leukoencephalopathy. *Eur J Neurol*. 2016;23(5):919-925. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26914970>.
98. Post MJ, Thurnher MM, Clifford DB, et al. CNS-immune reconstitution inflammatory syndrome in the setting of HIV infection, part 2: discussion of neuro-immune reconstitution inflammatory syndrome with and without other pathogens. *AJNR Am J Neuroradiol*. 2013;34(7):1308-1318. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22790252>.
99. Clifford DB. Neurological immune reconstitution inflammatory response: riding the tide of immune recovery. *Curr Opin Neurol*. 2015;28(3):295-301. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25887769>.
100. Miralles P, Berenguer J, Lacruz C, et al. Inflammatory reactions in progressive multifocal leukoencephalopathy after highly active antiretroviral therapy. *AIDS*. 2001;15(14):1900-1902. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/11579261>.
101. Safdar A, Rubocki RJ, Horvath JA, Narayan KK, Waldron RL. Fatal immune restoration disease in human



- immunodeficiency virus type 1-infected patients with progressive multifocal leukoencephalopathy: impact of antiretroviral therapy-associated immune reconstitution. *Clin Infect Dis*. 2002;35(10):1250-1257. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/12410486>.
102. Hoffmann C, Horst HA, Albrecht H, Schlote W. Progressive multifocal leukoencephalopathy with unusual inflammatory response during antiretroviral treatment. *J Neurol Neurosurg Psychiatry*. 2003;74(8):1142-1144. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/12876257>.
  103. Di Giambenedetto S, Vago G, Pompucci A, et al. Fatal inflammatory AIDS-associated PML with high CD4 counts on HAART: a new clinical entity? *Neurology*. 2004;63(12):2452-2453. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15623736>.
  104. Fournier A, Martin-Blondel G, Lechapt-Zalcman E, et al. Immune Reconstitution Inflammatory Syndrome Unmasking or Worsening AIDS-Related Progressive Multifocal Leukoencephalopathy: A Literature Review. *Front Immunol*. 2017;8:577. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28588577>.
  105. Martin-Blondel G, Cuzin L, Delobel P, et al. Is maraviroc beneficial in paradoxical progressive multifocal leukoencephalopathy-immune reconstitution inflammatory syndrome management? *AIDS*. 2009;23(18):2545-2546. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19907215>.
  106. Shahani L, Shah M, Tavakoli-Tabasi S. Immune reconstitution inflammatory syndrome in a patient with progressive multifocal leukoencephalopathy. *BMJ Case Rep*. 2015;2015. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26063110>.
  107. Middel A, Arends JE, van Lelyveld SF, et al. Clinical and immunologic effects of maraviroc in progressive multifocal leukoencephalopathy. *Neurology*. 2015;85(1):104-106. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26041329>.
  108. Stork L, Bruck W, Bar-Or A, Metz I. High CCR5 expression in natalizumab-associated progressive multifocal leukoencephalopathy immune reconstitution inflammatory syndrome supports treatment with the CCR5 inhibitor maraviroc. *Acta Neuropathol*. 2015;129(3):467-468. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25604548>.
  109. Crossley KM, Agnihotri S, Chaganti J, et al. Recurrence of progressive multifocal leukoencephalopathy despite immune recovery in two HIV seropositive individuals. *J Neurovirol*. 2016;22(4):541-545. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26727910>.